REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

The rejection of claims 89 and 93 under 35 U.S.C. § 102(b) as anticipated by Lipshutz et al., Biotechniques 19(3):442-447 (1995) ("Lipshutz") is respectfully traversed.

Lipshutz relates to a method of light-directed chemical synthesis to create high-density arrays of oligonucleotide probes, which can be used for detection of hybridized targets. In particular, this reference discloses the synthesis of an array of oligonucleotides in which linker molecules with a photochemically removable protective group are attached to a solid substrate. Light is directed through a photolithographic mask to specific areas of the surface, activating those areas for chemical coupling. The first of a series of nucleosides is incubated with the array, and chemical coupling occurs at those sites that have been illuminated in the preceding step. Next, light is directed to a different region of the substrate through a new mask, and the chemical cycle is repeated. The process is repeated.

In contrast, claim 89 (and its dependent claims 90-112) is directed to "[a] method of forming arrays of oligonucleotides on a solid support comprising: providing a solid support having an array of positions each suitable for attachment of an oligonucleotide; attaching to the solid support surfaces or linkers, suitable for coupling oligonucleotides to the solid support, at each of the array positions; and forming an array of a plurality of capture oligonucleotides on the solid support by a series of cycles of activating selected array positions for attachment of multimer nucleotides and attaching multimer nucleotides at activated array positions, wherein the multimer nucleotides are selected for attachment so that the capture oligonucleotides formed on the array hybridize with complementary oligonucleotide target sequences under uniform hybridization conditions" (emphasis added).

Lipshutz neither discloses nor suggests attaching multimer nucleotides at activated array positions, as required by claim 89 and its dependent claims. In contrast, Lipshutz teaches attaching single nucleosides to sites that have been illuminated in the preceding step. By serially attaching an oligonucleotide, as in Lipshutz, an array of 1,000 addresses would require over 40 days of around-the-clock work to prepare (see Specification at page 34, lines 19-21). Arrays containing short oligonucleotides of 8- to 10-mers do not have commercial applicability, because longer molecules are needed to detect single base differences effectively (see Specification at page 34, lines 21-23).

Lipshutz neither discloses nor suggests using multimer nucleotides which are selected for attachment so that the capture oligonucleotides formed hybridize to complementary oligonucleotides under uniform hybridization conditions, as required by the claims of the present application. In contrast, Lipshutz identifies the generation of signal from GC-rich and AT-rich probes (which have different hybridization strengths) in the same experiment as an "important challenge" to be met for broad implementation of the disclosed method (see page 47, col. 1, lines 21-30). This is an important distinction between Lipshutz and the claimed invention. In particular, the probes in Lipshutz's array carry the burden of both detecting a target nucleic acid and generating a signal correlated to detection of the target. Designing a plurality of capture probes to detect and signal detection of a plurality of different nucleic acid targets at one time on a single array (i.e. under uniform hybridization conditions) is a difficult task using Lipshutz's technology. Moreover, since Lipshutz's capture probes must accomplish the diverse tasks of detection and signaling, its system is particularly susceptible to producing false signals. By contrast, detection and signaling of such detection can be readily and accurately achieved with the device produced by the method of the present invention, because the above characteristics of the capture probes.

One example of how the device produced in accordance with the present invention achieves such improved results involves its use with ligase detection reaction ("LDR"). As shown, for example, in Figure 3 of the present application, the presence or absence of a particular base in a target nucleic acid sequence is detected by LDR using probes having target specific portions (shown as hatched). One of those probes has capture probe specific portion Z1, Z2, Z3, or Z4 (shown as solid) which does not bind to the target nucleic acid but is important in the subsequent step of array capture. When target nucleic acid is present, the probes are ligated and the sample is contacted with an array so that capture probe-specific portion Z1, Z2, Z3, or Z4 hybridizes to its complementary capture probes. When the target nucleic acid is in the sample during LDR (so that the LDR probes ligate), that ligation event will form a product having a marker which can be detected when that product is hybridized to a capture probe on the array at capture probe-specific portion Z1, Z2, Z3, or Z4. Use of a device produced in accordance with the present invention in an LDR process is only one example of how that device can be utilized. The important thing to remember is that, with that device, detection and signaling can be carried out separately, facilitating the array capture and detection of a plurality of different nucleic acids at one time.

In the March 9, 2005, final rejection (page 14), the following is stated with regard to the "under uniform hybridization conditions" limitation:

> [A] recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then, it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art.

Applicants have no real dispute with this commentary, because, as noted above, it is fully satisfied by the claimed invention. In particular, an array with capture oligonucleotides that hybridize with complementary oligonucleotide target sequences under uniform hybridization conditions clearly provides a structural distinction between that array and the array of prior art like Lipshutz. The October 4, 2005, advisory action mischaracterizes this assertion in arguing that the probes of the claimed invention and Lipshutz are the same, because the distinction is based on the **plurality** of capture oligonucleotides formed on the solid support as opposed to the **individual** capture oligonucleotides. As noted above, that structural distinction of claimed array achieves a beneficial performance difference from the prior art. The claimed method of making the array can also be distinguished on this basis. Specifically, the step of forming an array of a plurality of capture oligonucleotides on the solid support by attachment of multimer nucleotides where the multimer nucleotides are selected for attachment so that the capture probes formed on the array hybridize with complementary oligonucleotide target sequences under uniform hybridization conditions clearly amounts to the use of different positive manipulative steps than those employed by Lipshutz. If this were not the case, Lipshutz would produce the same array as applicants which is clearly not the case. Thus, the forming an array step of the claims is not just an inherent property or intended use, as suggested in the advisory action, but clearly distinguishes the claimed invention from this reference.

Accordingly, the rejection based on Lipshutz is improper and should be withdrawn.

The rejection of claims 89 and 93 under 35 U..C. § 102(b) as anticipated by Fodor et al., Nature 364:555-556 (1993) ("Fodor II") is respectfully traversed.

Fodor II relates to the synthesis of biological arrays by attaching linkers modified with photochemically removable protecting groups to a solid substrate. Light is directed through a photolithographic mask to specific areas of the surface effecting localized

photodeprotection. The first of a series of chemical building blocks (e.g., hydroxyl photoprotected deoxynucleosides) is incubated with the surface, and chemical coupling occurs at those sites which have been illuminated in the preceding step. Next, light is directed to a different region of the substrate through a new mask, and the chemical cycle is repeated.

Fodor II neither discloses nor suggests forming an array using capture oligonucleotides that hybridize with complementary oligonucleotide target sequences under uniform hybridization conditions, as required by the claims of the present application. Accordingly, for substantially the reasons noted above, the rejection based on Fodor II is improper and should be withdrawn.

The rejection of claims 89-93, 96-97, 109, and 111 under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 5,700,637 to Southern et. al., is respectfully traversed.

Southern discloses an apparatus and a method for analyzing polynucleotide sequences as well as a method of generating oligonucleotide arrays. The oligonucleotides forming the array are only disclosed to be formed from conventional nucleotides. Thus, Southern suffers from the same deficiencies as Lipshutz and fails to teach forming an array of capture oligonucleotides that hybridize with complementary oligonucleotide target sequences under uniform hybridization conditions, as claimed. Accordingly, the rejection based on Southern should be withdrawn.

The rejection of claims 89, 91, 93, 96, and 111 under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 5,837,832 to Chee et. al., is respectfully traversed.

Chee teaches arrays of nucleic acid probes on biological chips. The oligonucleotide probes used on the subject chips of Chee do not constitute capture probes in accordance with the present invention where the capture oligonucleotides on the array hybridize with complementary oliognucleotide target sequences under uniform hybridization conditions. Therefore, Chee is distinguishable from the claimed invention for substantially the same reasons noted above, and the rejection based on this rejection should be withdrawn.

The rejection of claims 89-97, 109, and 111-112 under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 5,510,270 to Fodor et al. ("Fodor I") is respectfully traversed.

Fodor I relates to a method for synthesizing and screening polymers on a solid substrate. The method includes providing a substrate which may include linker molecules on its surface. On the substrate or a distal end of the linker molecules, a functional group with a protective group is provided. The protective group may be removed upon exposure to

radiation, electric fields, electric currents, or other activators to expose the functional group. Using photolithographic methods, the protective group is removed in first selected regions and the substrate is contacted with a first monomer which reacts with the functional group. Thereafter, second selected regions are deprotected and exposed to a second monomer which reacts with the exposed functional group. These steps are repeated until the substrate includes desired polymers of desired lengths. Monomers may include amino acids, nucleotides, pentoses, and hexoses.

Fodor I neither discloses nor suggests forming an array using capture oligonucleotides that hybridize with complementary oligonucleotide target sequences under uniform hybridization conditions, as required by the claims of the present application. Therefore, Fodor I is distinguishable from the claimed invention for substantially the same reasons noted above, and the rejection based on this reference should be withdrawn.

The rejection of claims 89-94, 96-97, 109, and 111-112 under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 5,527,681 to Holmes ("Holmes") is respectfully traversed.

Holmes relates to methods, devices, and compositions for synthesis and use of diverse molecular sequences on a substrate. In particular, this reference discloses the synthesis of an array of polymers in which individual monomers in a lead polymer are systematically substituted with monomers from one or more basic sets of monomers. On the substrate or a distal end of linker molecules, a functional group with a protective group is provided. The protective group may be removed upon exposure to a chemical reagent, radiation, electric fields, electric currents, or other activators to expose the functional group. Using photolithographic methods, the protective group is removed in first selected regions and the substrate is contacted with a first monomer which reacts with the functional group. Thereafter, second selected regions are deprotected and exposed to a second monomer which reacts with the exposed functional group. These steps are repeated until the substrate includes desired polymers of desired lengths. Monomers may include amino acids, nucleotides, pentoses, and hexoses. Holmes neither discloses nor suggests forming an array using capture oligonucleotides that hybridize with complementary oligonucleotide target sequences under uniform hybridization conditions, as required by the claims of the present application. Therefore, Holmes is distinguishable from the claimed invention for substantially the same reasons noted above, and the rejection based on this reference should be withdrawn.

In view of the all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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